JAPANESE MEDICAL MATERIAL

THYMOPHOGEN

(Sodium 4-chlorthymol-phosphate)

Medical No. 230

24 May 1946

MEDICAL ANALYSIS SECTION
5250 Technical Intelligence Company
APO 500

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24 May 1946

THYMOPHOGEN

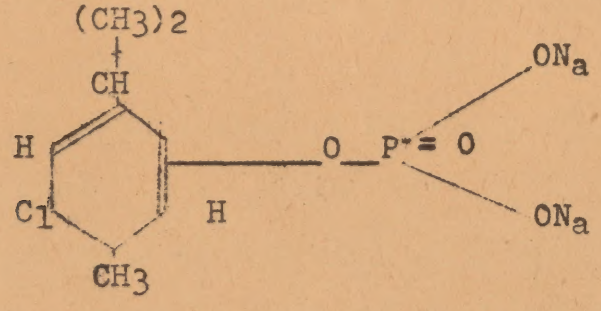
(Sodium 4-chlorthymol-phosphate)

SOURCE: Tokyo, Japan.

IMPORTANCE: Not previously reported. An organic compound for which bactericidal action against the tubercle bacilli is claimed. No identical product is listed in available American references.

DESCRIPTION: Six amber tinted ampuls, each containing 1.0 gm. of a white powder, are enclosed in a cardboard box.

SUMMARY OF GENERAL INFORMATION: Thymophogen is sodium mono 4-chlorthymol phosphate:



Thymophogen in itself is not bactericidal but is claimed to be decomposed in the body by phosphatase and the high hydrogen ion concentration of the infected area to liberate 4-chloro-thymol. This compound has the property of penetrating the lipoids which are in the tissues near the infection, thereby reaching the foci where its anti-tubercular action occurs.

It is available in the following forms and sizes:

Ampuls: 0.1, 0.2, 0.4, 0.6, 0.8, 1.0, 1.5, and 2.0 gm. Each is furnished in containers of either 6 or 36 ampuls.
Vials: 2.0, 5.0, and 25 gm.

The ampuls are intended for sterile injectable solutions in a 4 to 5% concentration in distilled water or glucose (5 - 10%). Parenteral dosage begins with 0.2 gm., administered daily or on alternate days, and is gradually increased to approximately 1.0 gm. A dosage table is included for use as a guide. The blood vessels receiving the injections of thymophogen become hardened if leakage occurs and in such cases a period of rest is prescribed to allow the blood vessels to renew their elasticity.

The powder (0.1 to 02%) is to be dissolved in physiological salt solution (1.0 to 1.5%) and vaporized for inhalation. No restriction is placed on the inhalation method of treatment.

A translation of the literature enclosed with the product is part of this report and includes its chemistry, pharmacology, indications, routes of administration, dosage, cautions, toxicology, packaging and manufacturer.

PHOTOGRAPHS:

Figure 1 - Closed package of Thymophogen

Figure 2 - Open package of Thymophogen

Figure 3 - Thymophogen literature

Figure 1 – Closed Package of Thymophogen

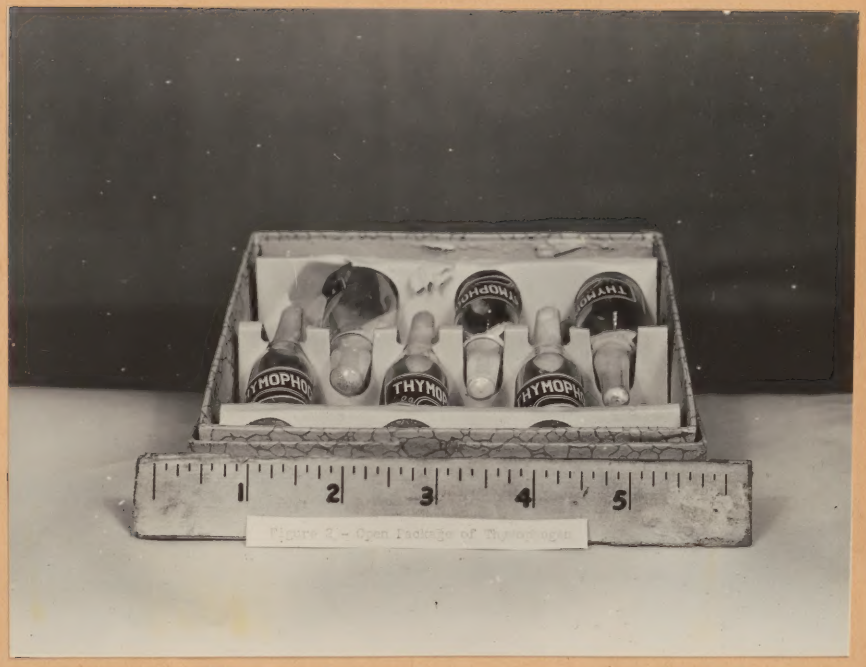


Figure 2 – Open Package of Thymophogen

北海道帝國大學醫學部 教授 有馬英二博士 實驗推奨
北海道帝國大學醫學部 助教授 鮎川武一博士 創製

結核化學療法特効新藥

特許 製法

チモフォーゲン

靜脈注射用 吸入並外用

THYMOPHOGEN

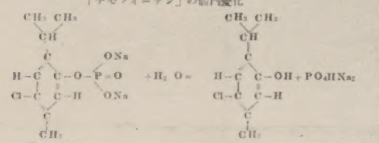
化學名 Mono-4-chlorthymyl-phosphorsaures Natrium

「チモフォーゲン」の製成及び性狀

「四・クロールチモール」の性狀並結核菌に對する殺菌作用

「チモフォーゲン」による結核化學療法の理論並に體内變化

「チモフォーゲン」の體内變化



Thymophogen (Mono-4-chlorthymyl-phosphorsaures Natrium)　　4-chlorthymol

「チモフォーゲン」の忍容性と副作用

「チモフォーゲン」の臨床效果

「チモフォーゲン」の適應症

「チモフォーゲン」靜脈内注射の用量並に注意

「チモフォーゲン」の外用並に吸入用としての治療領域及其の用法用量

包裝價格

靜脈用

Nr.1	0,1G.	6Amp. / 36Amp.	2,50 / 12,50
Nr.2	0,2G.	6Amp. / 36Amp.	3,20 / 17,00
Nr.3	0,4G.	6Amp. / 36Amp.	4,50 / 24,00
Nr.4	0,6G.	6Amp. / 36Amp.	5,70 / 30,50
Nr.5	0,8G.	6Amp. / 36Amp.	6,80 / 36,00
Nr.6	1,0G.	6Amp. / 36Amp.	7,80 / 42,00
Nr.7	1,5G.	6Amp. / 36Amp.	10,20 / 55,00
Nr.8	2,0G.	6Amp. / 36Amp.	12,50 / 66,00

吸入並に外用

2,0G	瓶入	2,00
5,0G	瓶入	2,50
25,0G	瓶入	10,00

「チモフォーゲン」用量表

製造發賣元 三星藥品株式會社

Figure 3 - Thymophogen Literature

TRANSLATION OF LITERATURE ACCOMPANYING THYMOPHOGEN

THYMOPHOGEN

Mono 4-chlorthymol-phosphorsaures natrium
A specific Tuberculosis chemotherapeutic.

For intravenous injection, inhalation and external use. Experimented and recommended by Dr. Eiji Arima, Professor in the Medical Department of the Hokkaido Imperial University.

Discovered by Dr. Takeichiro Ayukawa, Assistant professor in the Medical Department of the Hokkaido Imperial University.

THYMOPHOGEN is the product of the untiring effort of Dr. Ayukawa, who intended to cure tuberculosis for more than ten years. At the beginning of the study many tubercle bacilli bactericides were found. Among them 4-chlorthymol, a specific, not affected by the existence of albumen, was discovered. It can be used in living bodies. It resembles salvarsan and other arsenicals that can be used in living bodies although arsenic itself can not be used directly.

The chemical and bacteriological studies were carried on at the medical chemistry and the dermatology sections respectiv ely. One part of the report was already published in 1930. Due to ceaseless effort and studies, it has attained perfection as an anti-tuberculosis specific. Since 1934, Dr. Arima, professor of the 1st. internal department of the Hokkaido Imperial University, has performed many experiments on both the bacillus and with animals.

These excellent results were reported to the people at the 14th General Meeting of the Japanese Tuberculosis Association by a special speech given by the men on this research, Dr. Arima and Dr. Sasaki, one of the assistants at Arima's Internal Laboratory. The experiments were done at the pharmacological sections of surgery, gynaecology, and pediatry. (Published by Dr. Yoshida at the 34th Japan Gynaecology Association).

The results of supplementary experiments were published at the 15th General Meeting of the Japanese Tuberculosis Association by doctors and clinical doctors.

On November 11, 1937, at the autumn Extraordinary Meeting of the Hokkaido Medical Society, the following reports were published: "The Application of Medicine to Renal Tuberculosis" by Dr. Ryo Shiga, professor at the skin and urinary section of the Hokkaido Imperial University, "The Application of Under Mucous Membrane Injection for Tuberculosis of Fauces", by Bachelor Tsunehisa Yanai, professor at the otorhinolaryngology section, and "The Inhalation Treatment for Tuberculosis of Fauces", by Bachelors Nobuyuki Ozawa, Kakugoro Kondo and Kinji Kachi of the 1st internal section.

From April, 1-4, 1938, at the 16th Japan Tuberculosis Meeting held in Kyoto, several lectures and influential supplementary lectures were given.

In October, 1938, at the local meeting of Dai-Nippon Dermatology and Ureology Association in Osaka, the clinical results of this medicine against renal tuberculosis were presented by Dr. Nishimura and five other doctors of the medical department of the Osaka Imperial University.

In October, 1938, at the local meeting of Dai-Nippon Otorhinolaryngology Association, in Osaka, Dr. Furukawa of the Wakayama Public Hospital lectured on the reaction of the medicine toward tuberculosis of the fauces.

Following this, the gist of the action of this medicine was reported in the Japanese clinical medicine magazine "Clinical Medicine of Japan" issue of November, 1938.

In the December, 1938 issue of "Treatment and Prescriptions", Dr. Inui of the Miyagi-branch of the Japanese Red Cross, showed an example of this medicine applied to both tuberculosis of fauces and pulmonary phthisis.

In the January, 1939 issue of "Japanese New Treatments", a treatise connected with this remedy was published.

In the February, 1939 issue of the "Medical Experiments", we saw the treatise, "Experience in the use of Thymophogen to Surgical Tuberculosis, such as Caries, and Articular Tuberculosis".

In "Tuberculosis" vol. 17, No. 1, Bachelor Kinji Kazi, student at the 1st internal section of the graduate school of the Hokkaido Imperial University, published a treatise entitled "The Study of the Action of Thymophogen Preventing the Growth of the Bacteria of Tuberculosis".

All these facts have pronounced the accurate effect of this remedy, and it's practical effects have been proven widely.

COMPOSITION AND CHARACTER OF THYMOPHOGEN

This is a chemical compound with the following formula: * $(CH_3)_2CH.C_3H_2Cl.CH_3.O\ PO_3Na_2$ (Mono 4-chlorthymol-phosphorsaures natrium). It is a colorless, oderless, pin-like crystal with silky lustre. The actual drug appears as a white powder, easily soluble in water. Its water solution is weakly alkaline. It resists alkali but is easily hydrolyzed by acids or phosphatase of the body to 4-chlorthymol $(CH_3)_2CH.C_6H_2.Cl.CH_3.OH$ (cf. respective books).

NATURE AND ANTI*TUBERCULOSIS BACILLUS ACTION OF 4-CHLORTHYMOL

This is one phenol with a pleasant odor. The colorless crystal plates are insoluble in water, soluble in caustic alkali liquids, easily soluble in organic solvents, and it's solution has the special character of being lipoid soluble.

Its bactericidal action against the tuberculosis bacillus is so vigorous that it destroys the bacillus in concentrations of 1/100,000 - 1/1,000,000. If a 0.02% solution is used, it acts in less than one hour.

*(T.N. This is probably an error and should be corrected to read $(CH_3)_2\_CH\_C_6H_2\_Cl\_CH_3\_O\_PO_3Na_2$)

The principal reasons are:

(a) As it is lipoid soluble, it easily penetrates through the lipoid membrane of the tuberculosis bacillus. This can not be done by other bactericides.

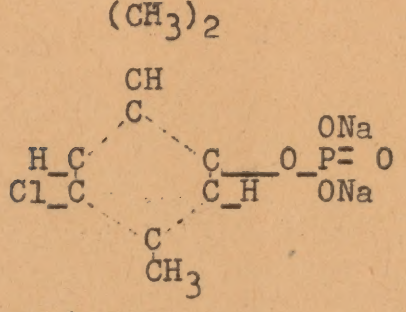
(b) It is not affected by the existence of albumen. It is clear, from reference sources, that both Guaiacol and Carvacrol, an isomer of thymol, haven't bactericidal action against tuberculosis bacillus.

THORY OF THYMOPHOGEN AND ITS PHYSIOLOGY

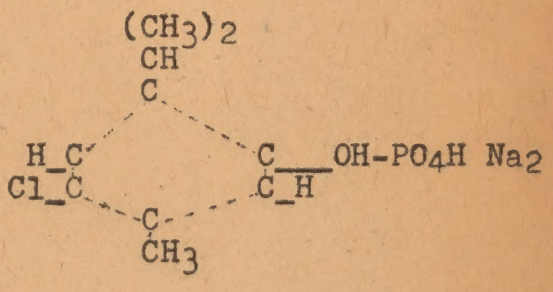
As the chemical name shows, it is an ester salt produced by reacting 4-chlorthymol with phosphoric acid, but in this state it has no bactericidal power at all.

When it is ingested into the living body it is hydrolyzed by phosphatase and by the high hydrogen ion concentration of the infected area. Then the 4-chlorthymol penetrates the lipoid which is in the tissue near the tubercular infections, and reaches the foci where it acts as a powerful bactericide.

The fact that the Thymophogen is easily decomposed in the infected part is well proven by the peculiar effects resembling fever which develope when an injection is made. This is why it is claimed by clinical doctors to be a diagnostic for infected areas.



Thymophogen
(Mono 4-chlorthymol-
phosphorsaures natrium)



4-chlorthymol

TRANSFORMATION OF THYMOPHOGEN IN THE BODY

The 4-chlorthymol which was formed by the hydrolysis of Thymophogen is excreted as conjugations of glucuronic and sulfuric acids.

ADMISSIBILITY AND SECONDARY REACTION OF THYMOPHOGEN

The composition as I wrote above is quite poisonless to the living body. At an experiment, we could not observe any secondary reaction after injecting intravenously 10 cc of a 20% solution (equal to 2.0 Gm. of powder) into a rabbit weighing 1.6 Kg. Judging from this it can be given to men without danger.

However, when one has many focal infections it is decomposed rapidly according to the reason above, so I warn you on its dosage when it is used in clinics. The maximum dosage for humans was found to be 2.0 Gm. of powder daily. If the amount is increased gradually, secondary reactions will not occur. There is no danger if a small quantity escapes from the vein.

We had better not use it when there are fractures of bones, because a remarkable reaction would occur in the living body owing to the sudden decomposition by phosphatase.

THE MEDICAL USE OF THYMOPHOGEN

You can expect the following effect in anti-tuberculosis treatment:

1. Recovery of the precipitation speed of red blood-corpuscles.
2. Speedy coagulation of blood.
3. Decreased tuberculosis bacillus in the sputum.
4. The febrifuge action.
5. The sedative and hypnotic action.
6. Increase of appetite.
7. Increase of weight.
8. Antitussive action.
9. Decrease of phlegm.

INDICATIONS

Pulmonary phthisis, tuberculosis of pulmonary lymph nodes, catarrh of the pulmonary apex, early infiltration, tubercular pleurisy, tubercular peritonitis, caries, tuberculosis of the kidney, glandular tuberculosis, nodular tuberculosis, tuberculosis of the bronchial tract, tuberculosis of sexual organs, skin tuberculosis, scrofula, asthma of the bronchi, tuberculosis of pharynx, uterine tuberculosis, tuberculosis of b one, anal fistula, and other tubercular conditions.

We can estimate it's value as a preventive by the fact that it destroys the bacilli that are injected into the test animals.

DOSAGES AND CAUTION IN THE INTRAVENOUS USE OF THYMOPHOGEN

Density: The suitable density is 4% to 5% in sterilized water or in a 5% to 10% solution of glucose. Allow the bubbles to break, and inject slowly and carefully into the vein.

Dosage: (Relation between reaction and dose) For Adult:

Begin with 0.2 Gm., to 0.4 Gm. (0.2 Gm. for females or serious cases) and watch for reactions. (In chronic cases we can hardly see any reaction with 0.2 Gm. to 0.4 Gm.). When large doses, such as 0.4 Gm., 0.6 Gm., 0.8 Gm., and 1.0 Gm. are reached, repeat the doses several times. The injections are to be given daily or on alternate days.

In case of internal infection such as pulmonary tuberculosis, continue the injection keeping the maximum dose at 1.0 Gm. but in case of external disease, such as caries, use 1.5 Gm. to 2.0 Gm. each time, though at times more than 2.0 Gm. may be used. However, you must remember that when it escapes from the blood vessel, the local area where it escaped becomes calloused. If leakage occurs, stop the injection. One series consists of 25 Gm. to 40 Gm. Allow the blood vessel to recover for a period of 10 to 30 days. Generally one series will satisfactorily improve the disease.

Occasionally, in case of severe weakness or when the reaction continues it is better to divide the series into several terms and have rest periods of 5 to 7 days. This method is also used when the disease is severe or chronic.

The maximum dosage: For internal use ordinarily 1.0 Gm., in very rare instances 1.5 Gm. For external use: 2.0 Gm. The required dose varies in each instance.

Reaction of injection: This is not a secondary reaction but an inevitable pharmacological reaction due to the destruction of the tuberculosis bacillus by 4-chlorthymol which was formed in the diseased part.

The outlook of the reaction: In 35 to 60 seconds after the injection the patient feels a tingling sensation, generally proportionate to the degree of the illness. In an infection in the lungs, the patient may be affected by irritation of the breast and light dyspnea, and occasionally by a headache. This will disappear in 5 to 10 minutes. Ordinarily the patient will sleep comfortably for 1 to 5 hours after the injection. Sometimes the whole body feels tired and a slight ache is present in the diseased area, but all these reactions disappear in a short while. Very rarely one is affected by a fever of 38° to 39°C for about 30 minutes after the injection. Ordinarily the temperature returns to normal in 3 to 5 hours. Rarely the patient is affected by a temporary decrease of appetite or a decrease of weight. We could not recognize any dangerous reactions during the injection of the large amount of the remedy. All these reactions decrease with each injection, until no reactions are observed. The patient will then begin to gain weight.

The relation between reactions and the increase of dose: Naturally the reaction depends on the constitution, the size of the infection, and the amount of the injection. Nevertheless, if a large amount (0.8 Gm. to 1.0 Gm.) is injected, it will produce a chill or fever without fail. To avoid these strong reactions, the injection should be started in small amounts, 0.2 Gm. for serious victims and 0.4 Gm. for general patients, increasing the amount slowly. Ordinarily we can observe some reactions in the first increased injection, but that will disappear as repeated injections of the same dosages are given. When the dose of 0.6 Gm. is reached, repeat the injection several times even if you can not recognize any reactions. If you increase the dosage suddenly when the dose of 0.6 Gm. or 0.8 Gm. is reached, severe reaction will appear.

If you observe a strong reaction, regardless of the amount you have been giving, diminish the amount of the injection and wait for the opportunity to increase it again.

The dosage after a rest: After 5 days of rest following a series, the first injection must be commenced from 1 or 2 units lower than the highest amount previously given. For example, give 0.6 Gm. if a 1.0 Gm. injection had been used before the rest. Of course, note must be taken on the reaction in the case of the injections after the rest, but the dosage will be increased comparatively rapidly to the highest amount before the rest.

Caution: This medicine must not be used together with intravenous injections of calcium preparations for at least 24 hours. Nevertheless, calcium preparations may be used externally or orally. No dangerous reactions have been noted in other oral medications.

Thymophogen for external and inhalation use, method of treatment, and dosage by these routes: Experience has proved the following, but treatment must be at the discretion of the doctor.

(a) For tubercular diseases of the bone-marrow, joints, anus, skin, lymphatic glands, etc., wash, or use gauze compresses, wetted in 0.2 to 1.0 % solution in physiological salt solution. A stronger solution may be used if reaction does not occur.

(b) For tuberculosis of the skin, use a 0.4 to 1.0 % ointment.

(c) For tuberculosis of fauces begin with 0.3 % and increase the strenght gradually. There are examples where a 10 % solution has been used. Inject 1 to 2 cc in small quantities subcutaneously in the infected area (use a special made large needle). Compresses with a small quantity of a local anesthetic are advantageous.

(d) Dosage for inhalation use: Applied for tuberculosis of fauces, pulmonary tuberculosis, lung gangrene, bronchial dilation, etc., by inhalation of steam. Dissolve 0.1 % to 0.2 % of this in 1.0 % to 1.5 % of physiological salt solution. Use about 50 cc per dose, twice a day.

Package and price for intravenous use.

#1	0.1 Gm.	6 Amp.	¥ 2.50	
		36 "	12.50	
#2	0.2 Gm.	6 "	3.20	
		36 "	17.00	
#3	0.4 Gm.	6 "	4.50	
		36 "	24.00	
#4	0.6 Gm.	6 "	5.70	
		36 "	30.50	
#5	0.8 Gm.	6 "	6.80	(sterilized,
		36 "	36.00	distilled water
#6	1.0 Gm.	6 "	7.80	is not supplied)
		36 "	42.00	
#7	1.5 Gm.	6 "	10.20	
		36 "	55.00	
#8	2.0 Gm.	6 "	12.00	
		36 "	66.00	

For inhalation and external use

2.0 Gm. Vial	¥ 2.00
5.0 Gm. Vial	¥ 4.50
25.0 Gm. Vial	¥16.00

Note: Each lot is sterilized and biologically tested to insure purity.

Table of dose of THYMOPHOGEN

This table is the standard dose. Individual doses must be computed by reaction, fever, severity of the disease and the prognosis.

The opinion of many doctors is that the maximum dose to be given is 0.6 Gm. for women and children, and 0.8 Gm. for men, and that this should be the maintenance dose until the cure is effected.

For external use, 2.0 Gm. should be considered the maximum dose.

ADULT DOSE TABLE

The 1st day 0.4 Gm. (0.2 Gm. for female or serious victims)

Fever present		Fever absent	
2nd day	0.2 Gm.	2nd day	0.4 Gm.
3rd day	0.2 Gm.	3rd day	0.4 Gm.
4th day	0.2 Gm.	4th day	0.4 Gm.
5th day	0.2 Gm.	5th day	0.4 Gm.
6th day	0.4 Gm.	6th day	0.6 Gm.
If the patient has fever use 0.2 Gm. and do not increase the amount.		If the patient has fever use 0.4 Gm. and do not increase the amount.	
7th day	0.4 Gm.	7th day	0.6 Gm.
8th day	0.4 Gm.	8th day	0.6 Gm.
9th day	0.4 Gm.	9th day	0.6 Gm.
10th day	0.4 Gm.	10th day	0.6 Gm.
11th day	0.6 Gm.	11th day	0.8 Gm.
If the patient has fever use 0.4 Gm. and do not increase the amount.		If the patient has fever use 0.6 Gm. and do not increase the amount.	
12th day	0.6 Gm.	12th day	0.8 Gm.
13th day	0.6 Gm.	13th day	0.8 Gm.
14th day	0.6 Gm.	14th day	0.8 Gm.
15th day	0.6 Gm.	15th day	0.8 Gm.
16th day	0.8 Gm.	16th day	1.0 Gm.
If the patient has fever use 0.6 Gm. and do not increase the amount.		If the patient has fever use 0.8 Gm. and do not increase the amount.	
17th day	0.8 Gm.	17th day	1.0 Gm.
18th day	0.8 Gm.	18th day	1.0 Gm.
19th day	0.8 Gm.	19th day	1.0 Gm.
20th day	0.8 Gm.	20th day	1.0 Gm.
21st day	1.0 Gm.	21th day	1.0 Gm.
If the patient has fever use 0.8 Gm. and do not increase the amount.			
22nd day	1.0 Gm.		
23rd day	1.0 Gm.		
24th day	1.0 Gm.		
25th day	1.0 Gm.		
26th day	1.0 Gm.		

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